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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds--Developing Products for Treatment
Docket Number-OOD-1318

Dear Sir or Madam:

Enclosed please find our comments to the above-reference guidance.

If you need additional information or clarification, please contact me.

Very truly yours,

Kay Mary Harrell

Kay Mary Harrell

OOD-1318

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Comments on Guidance for Industry
Chronic Cutaneous Ulcers and Burns Wounds and Developing Products for Treatment

Submitted by:
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I. Introduction

Guidance: The guidance "specifically addressees venous stasis ulcers, diabetic foot ulcers, pressure ulcers, and burn wounds." In addition, the first paragraph in II.A. broadens the applicable wounds to include donor sites.

Comment: Since the etiology of burn wounds differs extensively from the etiology, and in many cases the treatment of, venous stasis, diabetic, and pressure ulcers, consideration should be given to issuing a separate guidance for burn wounds and a separate guidance for venous stasis, diabetic, and pressure ulcers.

II. Claims

A. General Considerations

Guidance: The guidance states that the product's claim refers not only to the beneficial effects of a product, as determined through clinical investigations, but also to the type of wound for which a product is intended. Also, the guidance states that separate safety and efficacy data should be submitted for each wound type for which an indication is sought.

Comment: Since initial safety is based on toxicology studies of a pre-clinical nature and these studies are not done with human subjects, it should not be necessary to require separate pre-clinical toxicology studies to be submitted for each human wound indication. This section should be modified to clarify that separate safety data should be submitted only for Phase I clinical trials as the first demonstration of safety in patients with the wound type for which the indication is sought. Redundant animal safety testing should not have to be performed in support of each wound type for which an indication is sought. This would, in effect, constitute an unnecessary use of animals. See, *Guideline on Safety Pharmacology Studies for Human Pharmaceuticals.*

Guidance: The guidance invited comments regarding other appropriate wound claims, endpoints, and assessment tools.

Comment: A recent review ([2]) examined reports of the microbiology of pressure sores, diabetic foot ulcers, surgical wounds, burn wounds, sickle cell leg ulcers and venous leg ulcers and indicated that the certain organisms are commonly found in infected wounds, irrespective of their etiology. The review suggested that although other microorganisms are isolated, those most commonly found in infected chronic wounds are S. aureus, S. pyogenes, Enterococcus sp., P.

aeruginosa, coliforms, Bacteroides sp. and Peptostreptococcus sp., although the site of a wound may somewhat modify the microflora.

If a product is designed to assist in the resolution of an infected wound, the resolution of the infection appears to be germane to its healing, regardless of etiology. The ability to benefit the greatest number of patients, therefore, could arise if patients with infected chronic wounds were allowed to be studied as a cohort. In this scenario, resolution of the infection, as dictated by the study design, would be the appropriate outcomes measures.

While the ability to close the wound is of utmost importance, the goal of closure would be premature in light of the infection. To that end, studies to evaluate the resolution of infection and then time or rate of closure of each of the etiologies specified in the proposed guidance could be unduly onerous and could negatively impact the time to delivery and cost effectiveness of these products.

B. Claims Related to Improved Wound Healing

1. Incidence of Complete Wound Closure

   Guidance: The guidance states that a claim of complete wound closure for chronic, non-healing wounds is considered the most clinically meaningful of the claims related to improved wound healing.

   Comment: We concur; however, it should be noted that palliative situations do exist in which the alleviation of symptoms is more pressing and imperative to the patient's quality of life than the closure of the wound. In addition, due to the underlying disease state, condition, or prognosis of the patient, complete closure may not be possible. However, treatment of symptoms and partial closure may be of great benefit to the patient.

   Guidance: The guidance definition of complete closure is accompanied by the statement in the following paragraph that the clinical benefit of wound closure that lasts for a very brief time is limited. In addition, it states that the subjects remain on study and continue to be evaluated at least 3 months following complete closure.

   Comment: While it is well known that complete and sustained closure is an optimal outcome, complete closure alone may not be the most meaningful measure. Indeed, it may not be possible given a patient's underlying condition. Also, it is unclear whether the three month data will be utilized as pivotal in the approval process and whether it be required for all phases of the clinical studies. If studies to support claims of the durability of closure at 3 months following treatment are required to provide statistical efficacy, the number of patients required at the initiation of the study will be vastly augmented and the cost of these studies will be increased.

   Guidance: The third paragraph in this section indicates that the measurement of partial healing may be acceptable in supporting efficacy claims, but also

indicates that these measurements in their own right are not considered acceptable for wound healing claims. It concludes by stating that "*partial healing that facilitates surgical closure* can be an acceptable claim".
Comment: The guidance should state that measurement of partial healing may be used in support of efficacy determinations when complete wound healing claims are being sought and that acceptability of partial healing measurements as primary evidence in claims related to facilitation of closure of all types of wounds is appropriate.

2. Accelerated Wound Closure
   Guidance: Accelerated closure is defined as "a clinically meaningful diminishing of the time until complete closure occurs."
   Comment: It should be noted that the possibility exists that clinically meaningful decrease in time to closure is possible without significantly reducing the time to complete closure. If, for instance, a product's average time to closure is 10 days faster than the control, but the statistical analysis indicates a p value of 0.12, the product should merit approval. Clearly, an average decrease in closure of 10 days has considerable impact on the patient's ability to return to daily activities and ability to afford treatment.

   Guidance: The second paragraph of this section appears to state that the claim that can be obtained by performing clinicals as per section 1 will be "improved incidence to closure."
   Comment: The claim of "accelerated wound closure" appears to be an option only when a study is designed such that the incidence to closure is the same in both arms AND the trial product has a faster time to healing than the product used in the other arm. It does not appear that good wound care would be one of the two arms. Studies designed in this manner may be unduly cumbersome because of the sponsor's need to find a product that has an incidence of closure similar to its own.

4. Improved Quality of Healing
   Guidance: The guidance appears to equate improved quality of healing with improved cosmesis.
   Comment: Improved quality of healing, as defined by improved functionality or quality of life, may be possible without improved cosmesis. While an excellent cosmetic result is desired, in many situations an improved functional result is even more desirable.

C. Other Considerations Related to Improved Wound Care

Guidance: The guidance states that "products intended for wound management may provide important patient benefit without improving the incidence or timing of closure relative to standard care" and then discusses wound infection control, debridement, wound pain control, and other wound care claims.

Comment: It is unclear whether wound infection control, debridement, wound pain control, and other wound care claims (e.g., improved quality of life) would be claims that could be obtained independent of the claims listed in Section B. (incidence of complete wound closure, accelerated wound closure, facilitation of surgical closure, and improved quality of healing). The claims listed in Section C. should be listed individually in Section B. and should be claims that could be obtained, if supported by appropriate clinical testing.

1. Wound Infection Control
   Guidance: Guidance states that "primary efficacy outcome for topical anti-infective wound products can be either healing or control of infection" and that both of these should be assessed.
   Comment: The product may control or resolve the infection in order to facilitate healing; however, healing, per se, may not be outcome of use of the product. Since infected wounds do not heal, the first step should be resolution of the infection, and studies could be designed only to evaluate this portion of the wound healing process. Safety of the product can be readily ascertained during this portion of the study with respect to adverse events, etc. Once the infection is resolved, the wound healing can be directly related to the underlying etiology and should be evaluated separately.

2. Debridement
   Guidance: The guidance specifies that a reasonable endpoint for a debridement claim might be a thorough removal of necrotic tissue (e.g. produces a wound bed suitable for grafting).
   Comment: The example is appropriate for burns, but not necessarily for other types of cutaneous ulcers. Additional examples for cutaneous ulcers include removal of all eschar or slough.

   Guidance: The guidance states that the primary efficacy endpoint is debridement equivalent to that produced by standard mechanical/surgical procedures.
   Comment: The statement implies that other forms of debridement are not viable. It is well known in the wound care field that the technique selected for wound debridement is dependent upon the urgency, risk of infection and condition of the patient ([4]). Pain is a frequently neglected consideration and should also be considered. The AHCPR Clinical Practice Guideline #15, Treatment of Pressure Ulcers, states, "Regardless of the method [of debridement] selected, the need to assess and control pain should be considered." ([1])

   Chemical and autolytic debridement for cutaneous ulcers, while not as expedient in the removal of necrotic tissue, have a considerable history with respect to efficacy, particularly in instances were a patient may not be a candidate for surgical debridement. ([3]) These modalities are well renown for their ability to address other clinically relevant endpoints such as pain and

blood loss ([3]). These endpoints, therefore, are acceptable as primary endpoints. In addition, chemical debridement has been long shown to be a safe and useful modality for in the treatment of burn patients.

Guidance: The guidance appears to suggest that mechanical/surgical procedures should be utilized as the standard by which to measure new product efficacy.
Comment: Commonly used mechanical debridement modalities such as "wet-to-dry" and "wet-to-moist" dressing changes are often components of good wound care and should be acceptable for use in a control arm. Sharp debridement should not be the only acceptable alternative. Also, if sharp debridement would be the only form of debridement to be utilized, then approval of other less aggressive forms of debridement should not be based on a time to complete removal of necrotic tissue alone.

Guidance: The last statement in this section suggests that cosmetic outcome and not impairing healing status are equal.
Comment: These two outcomes are very different and should not be linked. The premise is that the patient would find any type of closed wound more cosmetically pleasing than an open one.

3. Wound Pain Control
   Guidance: The guidance states that the effect of pain control products on healing is an important safety outcome.
   Comment: We agree; however, these products may have no effect on healing, and this section should provide that there is to be no measurable detrimental effect on healing. Furthermore, it is assumed that the demonstration of this lack of effect is to be incorporated into the clinical study design in some fashion. It would be helpful to have more specific guidance as to how to best achieve this goal to satisfaction of the Agency.

4. Other Wound Care Claims
   Guidance: This section includes "certain aspects of daily living not already captured by any of the previously described outcome measures...".
   Comment: Additional outcome measures could benefit from mention of the importance of quality of life measures, including odor relief. Consideration should be given to include more specific additional types of indications as examples.

III. **Preclinical Considerations**

Guidance: The guidance states that wound models may be helpful in establishing pharmacological responses.
Comment: There is no mention of the need for validation of in vitro or in vivo models to demonstrate their relevance to particular wound types for which approval is sought. Animal and non-animal models need to validated by some

means both for the demonstration of efficacy as well as toxicity particularly when the exposure is to wounded, burned or otherwise damaged skin.. Biodistribution data may or may not be meaningful when done in animal species depending on the chemical nature of the active ingredient and the model selected. This section should indicate perhaps the desirability of having this data but that requirements for preclinical biodistribution or pharmokinetic studies in animals will be made on a case by case basis by the Agency. Assuming that animal model data would always be required would not seem scientifically tenable. Likewise, carcinogenicity, reproductive and developmental toxicology studies should be required on a case by case basis depending clearly on the patient population to be treated and the indication sought. Genotoxicity testing may or may not be useful depending on the chemical nature of the active ingredient and also should be required only when it is feasible to perform these tests.

IV. Clinical Trial Considerations

C. Assessment/Quantification

Guidance: The guidance states that tools to assess clinical endpoints should be both "prespecified and standardized across clinical sites".

Comment: While it is desirable to standardize all aspects of clinical studies, the value of standardizing the camera lighting is questionable from a practical standpoint. Standardization of the photographic and wound imaging procedures should suffice. By calling out lighting conditions, it is envisioned that the investigator may be required to document these conditions prior to each photograph. This would obviously be of minimal benefit, but of considerable encumbrance, to the desired goal of developing products to assist in the healing of chronic ulcers.

E. Standard Care

1. Standard Care Considerations for Chronic Cutaneous Ulcers

Guidance: The guidance states that establishment of adequate circulation for arterial ulcers is a parameter for consideration.

Comment: Establishment of adequate circulation for arterial ulcers is paramount for all types of wound healing. Evaluation of this parameter should be considered standard for treatment of all, and not just arterial, ulcers.

a. Debridement

Guidance: The guidance states: "To avoid bias and confounding of treatment effect, ulcer debridement should precede evaluation of ulcer extent and infection. Enzymatic debriding agents, like other concomitant topical products, can confound results in wound product trials and generally should be avoided."

Comment: It is agreed that ulcer debridement should precede evaluation of an ulcer. Debridement of the ulcer is, as stated previously in the text, critical to the closure of the ulcer. The guidance presupposes that the only acceptable form of debridement is via mechanical/surgical

modalities and that chemical debridement is not a viable method. The final statement above suggests that enzymatic debriding agents are not viable products. This is clearly not the case as the use of enzyme debriding agents is the standard of care when patients are incapable of undergoing more aggressive means ([3]).

If an enzymatic debrider is incorporated into a study as standard of care, it will not confound results as long as it is not applied concomitantly with the test product. Wound healing occurs in several phases, and often different products are utilized to address these different phases. It is neither unfeasible nor poor study design if, for instance, an enzymatic debrider was utilized to remove the eschar and slough prior to treatment with a wound accelerating product.

Guidance: The guidance states that, "the need for additional debridement, performed after study treatment has started, may indicate product-induced wound deterioration."
Comment: It is well known that wound debridement usually results in wounds getting larger([3,4]) prior to decreasing in size and that, particularly in diabetics, it may be required more than once during the course of treatment. The need for *excessive* additional debridement rather than solely additional debridement may be a more appropriate guideline for indication that product-induced wound deterioration is occurring.

Due to their mode of action, enzymatic debriding agents may required extended periods (up to six weeks) of treatment. The language in the proposed guidance allows for the possibility that because of the protracted time frame enzymatic debriding agents may inadvertently be misconstrued as resulting in product-induced wound deterioration when in fact they are working as per design. Comments to acknowledge this case should be included in the text.

d. Infection
Guidance: The guidance states that "a high incidence of true infection (as opposed to colonization) is present for diabetic foot ulcers".
Comment: Appropriate reference citations would be of benefit to the industry and could provide important information such as what consists of 'a high incidence' in this population.
As indicated earlier, the concomitant use of topical antimicrobials will confound the analysis of the data. It should be recognized, however, that a topical antimicrobial may be acceptable for used as an integral element in good wound care during the "run-in" period.

e. Wound Cleansing
Guidance: The guidance states that "some cleansers retard healing, or can cause irritation and sensitization".

Comment: Wound cleansing removes bacteria and surface contaminants. Commercial cleansers often are augmented with mild detergents that assist in wound care and preservatives that prevent microbial colonization. While normal saline is perhaps the most physiological agent for wound cleaning, it seldom contains preservatives and is subject to contamination once opened. The guidance should provide that any cleanser could be used as long as it does not retard wound healing.

f. Nutritional Support

Guidance: The guidance states that caloric intake and metabolic status should be capture in the CRFs.

Comment: The necessity of capturing nutritional support data for products with no metabolic effects should be supported with references and it is unclear whether the Agency expects this to be considered as a covariate in the analysis.

F. Safety Considerations

1. Effects of the Product on the Wound

Guidance: The guidance indicates that repeat debridement is a result of deterioration of wounds.

Comment: Comments regarding the relationship between product-induced deterioration of the wound and whether or not the wound requires repeated debridement and/or increases in ulcer size have been made previously above.

V. Attachment

Guidance: The guidance states that topical products for the treatment of wounds should be sterile.

Comment: It is well known that uninfected wounds are colonized. The guidance itself alludes to these distinctions in Section E.1.d. The necessity of requiring sterile packaging of wound care products on the basis of avoiding introduction of exogenous microorganisms is strongly questioned. Well-preserved products meeting microbial challenge tests are standard in the industry and are capable of delivering their contents in a manner that will not introduce organisms

Sterile products themselves, when not packaged as single-use units, run the risk of allowing for introduction of exogenous microorganisms. The presence of preservatives in commercial wound cleansers, for instance, is one of the keys to making them superior to sterile normal saline. Should an unfortunate exposure to microbes occur, the preserved commercial wound cleansers have the capability of controlling the organisms, the saline does not.

VI. References

1. Bergstrom, N., Bennett, M. A., Carlson, C. E., and et al. Treatment of pressure ulcers. Clinical Practice Guideline, No.15. AHCPR Publication Number 95-0622. 1994. Rockville, MD, Department of Health and Human Service, Public Health Service, Agency for Health Care Policy and Research.

2. Bowler, P. G. The anaerobic and aerobic microbiology of wounds: A review. Wounds 10[6], 170-178. 1998.

3. Kennedy, K. L. and Tritch, D. L.: Debridement. In Krasner, D. and Kane, D. (eds),Chronic Wound Care: A Clinical Source Book for Healthcare Professionals, Second Edition,2 ed., pp. 227-234. Wayne, PA, Health Management Publications, Inc., 1997.

4. Rolstad, B. S. and Harris, A.: Management of deterioration in cutaneous wounds. In Krasner, D. and Kane, D. (eds),Chronic Wound Care: A Clinical Source Book for Healthcare Professionals, Second Edition,2 ed., pp. 209-218. Wayne, PA, Health Management Publications, Inc., 1997.

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Karl-Heinz "Fiete" Klenz – Specializing in the 100-meter breaststroke and 100-meter/200-meter freestyle, Klenz is training for a spot on the German Nationa for the 2000 Olympic Games in Sydney, Australia. He has worked at UPS for three years and is currently a part-time preloader in Leipzig, Germany. He is a global UPS Athlete Training Assistance Program (ATAP), which provides employee-athletes with the support they need to pursue their Olympic dreams.